REMARKS

1. Status of the Claims

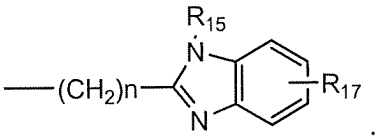
Claims 23, 24 and 34 as currently amended, claims 25-29 as originally filed, and claims 32 and 33, as previously presented, are pending.

No new matter has been added.

2. The First Rejection Based on 35 U.S.C. § 112, First Paragraph

Claims 23-29, 32-34 stand rejected as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, First Paragraph. Upon reviewing the Office's discussion of the Wands factors (*In re Wands*, 8 USPQ2d 1400, 1404 (CAFC 1988)), it is clear that the Office believes that the breadth of the claims is too great, when considered in light of the disclosure in the application as filed. Applicants respectfully disagree, but in order to expedite prosecution of this application and its ultimate issuance as a patent, they have amended the claims as follows.

In claims 23 and 34, the variable R_4 was amended to include only substituents of the formula:



As a result, variables R_7, R_8, r_9, R_{10}, R_{11}, R_{12}, R_{13}, and R_{14}, were canceled.

In claims 23 and 34, the definition of the variable "X" was amended by removing "S" (sulfur).

Claim 24 was amended by removing the final two structures.

Other minor, typographical errors were also fixed.

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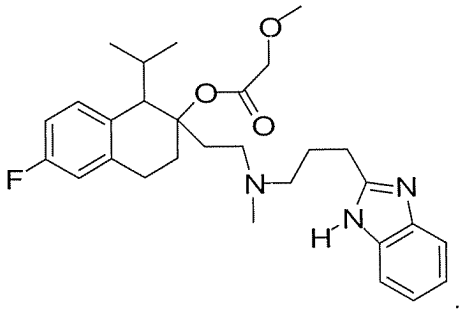
Based on the above amendments, it is clear that the breadth of the claims has been significantly reduced, and as a result, the Office's concerns based on the claim scope have been addressed.

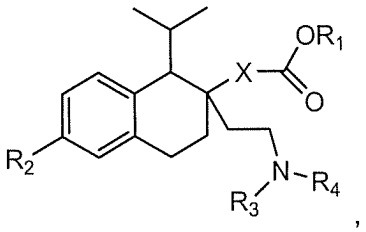
The Office also seems concerned because the Art is alleged to be not predictable and no "factual evidence or testing results" showing efficacy as calcium channel blockers is provided. The Office further states that the claimed compounds are not mibefradil analogs.

Applicants submit that the claims as amended encompass methods of using compounds that are structurally similar to mibefradil, and would be expected by one of ordinary skill in the art to have biological activity similar to that of mibefradil.

The structure of Mibefradil is as follows:



The structure from independent claim 23 is:



where X=a bond, $(CH_2)_n$, O, or $O(CH_2)_n$, wherein n=1-6;

R_1=C_{1-6} alkyl, optionally substituted with OH or NH_2;

R_2=F or $COOR_5$,

wherein R_5 is C_{1-6} alkyl, optionally substituted with OH or NH_2;

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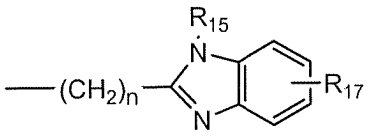
R_3=CH_3 or $(CH_2)_n$--$COOR_6$, wherein n=1-6 and R_6 is C_{1-6} alkyl, optionally substituted with OH or NH_2;

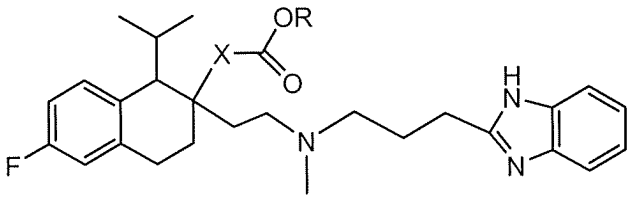
R_4= 

R_{15}= $(CH_2)_nCOOR_{16}$,

R_{16}=C_{1-6} alkyl, optionally substituted with OH or NH_2, and

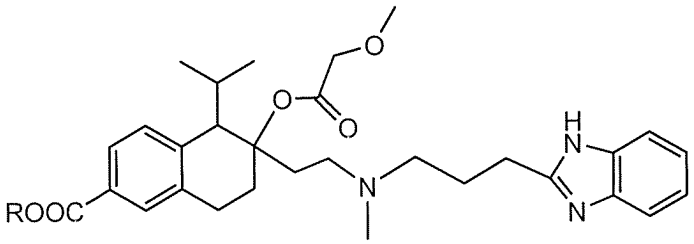
R_{17}=not present or $COOR_{18}$ wherein R_{18} is C_{1-6} alkyl, optionally substituted with OH or NH_2, and wherein n=1-6.

The structures from independent claim 24 are:

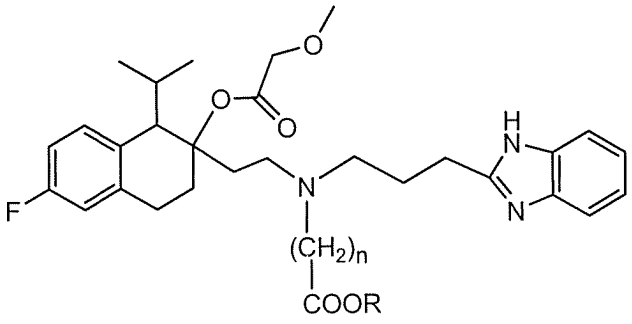


X=bond, CH_2, or OCH_2

R=lower alkyl optionally substituted OH or NH_2;



R=lower alkyl optionally substituted by OH or NH_2;



n=1 to 3

R=lower alkyl optionally substituted by OH or NH_2; and

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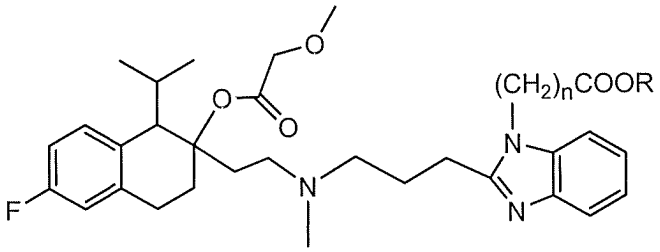
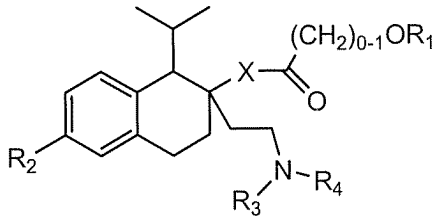


n=1 to 3

R=lower alkyl optionally substituted by OH or NH_2.

The structure from claim independent claim 34 is



,

where the definitions of the variables are similar to those in claim 23.

Upon reviewing the structure of mibefradil (above) and the structures from the independent claims, it is clear that the claimed structures were not randomly picked, but are structurally related to mibefradil. They have the same tetrahydrodecalin core with substitution at positions 1, 2, 2, and 6. Further, they all have the isopropyl group at position 1. The variable R_4 covers the same heteroaryl group as in mibefradil, and the variable X also encompasses groups that are related to those in mibefradil. The substitution at positions 2, 2, and 6 are also related to those of mibefradil, albeit, while being novel and non-obvious. One of ordinary skill in the art, comparing the structures of the compounds encompassed by the claims and that of mibefradil, would expect the compounds to have similar biological activity because they are structurally similar.

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In light of the above structures, the Applicants submit that this narrow facet of the Art is predictable; the amended claims are narrowly crafted to encompass methods using compounds that are similar to a known, biologically active agent. Applicants further note the following.

The lack of factual evidence does not mean the claims lack enablement. As stated in the MPEP, section 2164.02 of the eighth edition, revision 3, dated August 2005, where "Working Example[s]" in the context of enablement are discussed, the following is stated:

> "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)."

The Applicants have taught how to make the compounds encompassed by the claimed methods (see the figures), and one of ordinary skill in the art would recognize the structural similarity of the compounds encompassed by the claims and mibefradil. Further, one of ordinary skill in the art would readily know how to prepare, determine and administer the appropriate dose. As a result, undue experimentation is not required and one of ordinary skill in the art could readily practice the claimed invention.

In section 2164.04 of the MPEP, the following is also stated:

> "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

Then in section 2164.01(b) the following is stated:

> "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied."

Such is the situation here. The Applicants have taught how to make and use the invention, and the claims correspond in scope to the Applicants teaching. Further, the structural similarity

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between mibefradil and the compounds encompassed by the claims precludes any claim of "doubt[ing] the objective truth" of the specification. Consequently, the application is enabled.

Furthermore, the amount of experimentation necessary is not undue. The Office asserts that one of ordinary skill in the art would have to 1) envision a compound to test, 2) prepare a dosage, 3) determine the duration of treatment, 4) determine how to administer the treatment, 5) test the compound, and 6) study the toxicity of the compound. Applicants submit that all of the above do not equate to undue experimentation.

As stated in the MPEP in section 2164.01 on page 2100-193:

> "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774, F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)."

Applicants submit that the experimentation identified by the Office is not undue; it is routinely carried out in the pharmaceutical industry. It may be complex, but it is not undue.

Further, in section 2164.06(b), on page 2100-203 of the MPEP, the following is stated:

> "(C) In *in re Bundy*, 642 F.2d 430,434, 209 USPQ 48, 51-52 (CCPA 1981), the court ruled that appellant's disclosure was sufficient to enable one skilled in the art to use the claimed analogs of naturally occurring prostaglandins even though the specification lacked any examples of specific dosages, because the specification taught that the novel prostaglandins had certain pharmacological properties and possess activity similar to known E-type prostaglandins."

This is the present situation. The known, biologically active compound that is structurally related to the compounds encompassed by the method claims, acts as a starting point that enables one of ordinary skill in the art to begin the routine testing that is needed in order to determine appropriate dosages, routes of administration, etc.

As for toxicity testing, the MPEP, in section 2164.05, on page 2100-198, states:

> "However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. See Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir.

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1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].")"

Based on the above, it is evident that toxicity testing, which would be required by the FDA before clinical trials, is not required by the PTO in order to prove enablement. Toxicity testing is "more properly left to the [FDA]." *Id.* Consequently, toxicity testing should not be considered when determining whether undue experimentation is requried.

In light of the above, it is clear that potential toxicity should not preclude patentability of the claimed methods. Applicants submit that the patent laws do not exclude potentially toxic compounds; that is for the FDA to do. Consequently, toxicity testing should not be considered.

After considering all of the above, the Applicants submit that the enablement rejection is moot, and they request that it be withdrawn.

3. The Second Rejection Based on 35 U.S.C. § 112, First Paragraph

Claim 34 stands rejected for allegedly containing new matter in the form of a proviso, which removes any overlap with the Branca et al. reference (U.S. Patent No. 4,808,605.) In response, the applicants have amended claim 34 by canceling the proviso and requiring R_3 to be "$(CH_2)_n$--$COOR_6$, wherein n=1-6 and R_6 is C_{1-6} alkyl, optionally substituted with OH or NH_2." Support for this amendment can be found in the figures as filed. Specifically, see Figure 5. In light of these amendments, Applicants submit that this rejection is moot, and they request that it be withdrawn.

4. The First Rejection Based on 35 U.S.C. § 103

Claims 23-25 and 32-33 stand rejected as allegedly being obvious over Branca et al. Specifically, the Office asserts that Branca discloses compounds where R_3 is loweralkoxy-lower-alkylcarbonyloxy and that such compounds are homologs of the currently claimed compounds. Applicants respectfully disagree; the compounds are not homologs.

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Compounds of the formula –O-$COCH_2OR_1$ as disclosed in Brana are not homologs of the currently claimed compounds, which have the formula –O-$COOR_1$. Brana contains a –CH_2- spacer, where the pending claims do not. Furthermore, the compounds of Brana and the claimed compounds will have different chemical properties, which contradicts the Office's position that "Chemists knowing the properties of one member would in general know what to expect in adjacent members (*in re Henze*, 85 USPQ 261, 261 (CCPA 1950))." As such, the compounds cannot be homologs.

To further illustrate their point, Applicants submit the following example, which they believe is analogous to the present situation: a phenyl group (no –CH_2- spacer) and a benzyl group (which has a –CH_2- spacer), differ by a –CH_2- spacer, but they are not homologs because they have different chemical properties. In contrast, benzyl (which has a –CH_2- spacer) and phenethyl (which has a –CH_2-CH_2- spacer), differ by a –CH_2- group, but they have similar chemical properties; therefore, they are homologs.

Since the Brana compounds and the compounds encompassed by the claims are not homologs, claims 23-25 and 32-33 are not obvious.

As a result, the Applicants respectfully submit that the rejection of these claims based on 35 U.S.C. § 103(a) is moot, and they request that it be withdrawn.

5. The First Rejection Based on 35 U.S.C. § 103

Claims 23-25 and 32 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kazuhisa et al (JP 11035483), and in particular, the compound with registry number [220-873-01-8]. Applicants respectfully disagree.

As stated by the Office, Kazuhisa discloses a compound of the formula "–X-COCH2OR1, whereas the instant compound has –X-COOR1" (emphasis in the original). The Office then concludes that the compounds are homologs. For the same reasons identified

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above, Applicants submit that the compounds are not homologs and therefore, the compounds encompassed by the claims are not obvious. As a result, the Applicants respectfully submit that the rejection of these claims based on 35 U.S.C. § 103(a) is moot, and they request that it be withdrawn.

CONCLUSION

Applicants respectfully contend that all requirements of patentability have been met. Allowance of the claims and passage of the case to issue are therefore respectfully solicited.

Should the Examiner believe a discussion of this matter would be helpful, he is invited to telephone the undersigned at (312) 913-2114.

Respectfully submitted,

Date: July 18, 2006

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